بسم الله الرحمن الرحيم

University of Khartoum
Graduate College
Medical and Health Studies Board

Histopathological Patterns of Endometrial Biopsies in Patients with Postmenopausal Bleeding

By

Nada Eldesougi Ahmed Elmukhtar

MBBS (Ahfad University for Women, 2003)

A thesis submitted in partial fulfillment for the requirements of the Degree of Clinical MD in Pathology

Supervisor

Prof. Bashir Ibrahim Mukhtar
MBBS, F.R.C.Path.
Professor of Pathology
Faculty of Medicine
University of Khartoum

2010

قال تعالى:

﴿وقل رب زدني علماً﴾

صدق الله العظيم

سورة طه

الآية (114)

CONTENTS

Dedication

To whom I will be for ever indebted beloved father and family.

Acknowledgement

I must first express my gratitude and deepest thanks to my supervisor ***Prof. Bashir Mukhtar****, for his great help, support and for making conduction of this study possible.*

Especial thanks and great appreciation are due ***Dr. Maria Satti****, for her guidance and kind help.*

I am most grateful to my dear ***sister "Nihad"*** *for her encouragement and unlimited support.*

ABBREVIATIONS

AGU	Atypical Glandular cell of Undetermined Significanc
BMD	Bone Mineral Density
CAD	Coronary Artery Disease
D&C	Dilatation and Curettage
ET	Estrogen Therapy
HNPCC	Hereditary Non Polyposis Colorectal Cancer
OC	Oral Contraceptive
PEPI	Postmenopausal Estrogen Progestin Intervention
PID	Pelvic Inflammatory Disease
PMB	Post Menopausal Bleeding
POCS	PolyCystic Ovary Syndrome

LIST OF TABLES

LIST OF FIGURES

Page No.

ABSTRACT

Objectives: This is a retrospective crossectional study designated to describe the histopathological patterns of endometrial biopsies in postmenopausal bleeding (PMB) and to estimate the risk of endometrial cancer in endometrial biopsies taken from women presenting with PMB.

Materials and Methods: The study included 146 endometrial biopsies taken from women presenting with PMB at National Health Laboratory during the period from January 2009-June 2010.Data on procedure of endometrial sampling and pathological findings were obtained from files of the National Health Laboratory on predesigned questionnaire, slides, blocks and histopathology reports were revised by the investigator and supervisor .Results obtained were analysed using SSPS soft ware.

Results: The procedure of endometrial sampling was dilatation and curettage in 95 (65.06%) of biopsies, hysterectomy in 46 (31.50%) and polypectomy in 5(3.44%)of patients.

Benign lesions constituted 71.9% with endometrial polyps being the most frequent pattern (19.9%). Malignant lesions were diagnosed in 15.8% of biopsies, while 12.3% of endometrial biopsies were inadequate for interpretation.

Endometrial hyperplasia without atypia was found in 17.8% of endometrial biopsies; of which 84.62% were simple hyperplasia and 15.38% were complex hyperplasia. Endometrial cancer was diagnosed in 15.8% of endometrial biopsies with endometrioid adenocarcinoma being the most common histolopathological type (73.9%), 41.2% were poorly differentiated adenocarcinoma. Other patterns included proliferative endometrium, atrophic

endometrium, and chronic endometritis were present in 11%, 7.5% and 4.8% respectively.

Conclusion: The majority of histopathological findings in PMB were benign lesions (71.9%).Among the benign lesions endometrial polyps were the most predominant pattern. The malignancy risk of endometrial cancer was found to be 15.8%.

مستخلص

الاهداف :هذه دراسه قهقريه مقطعيه صممت للتعرف غلى التغيرات المرضيه فى الانسجه فى العينات من بطانه الرحم فى نزف ما بعد الاياس وتقدير خطر سرطان بطانة الرحم في العينات الماخودة من بطانة الرحم من النساء اللاتي اتين بنزف مابعد الاياس.

منهجية البحث: اشتملت الدراسه على6 14 عينه من بطانه الرحم اخذت من النساء اللاتى اتين بنزف ما بعدالإياس بالمعمـل القومى الصحى خلال الفترة ما بين يناير 2009م وحتى يونيو 2010م. تم الحصول على المعلومات عن وسيله اخذ العينه من بطانه الرحم والنتائج المرضيه من ملفات المرضي بالمعمل القومى الصحى باستخدام استبيان معد مسبقاً. ومن ثم تمت مراجعة الشرائح، المقاطع، وتقارير الأنسجة المريضة بواسطة الباحث والمشرف . ومن ثم حللت النتائج إحصائيا باستخدام برنامج الحاسوب SSPS.

النتائج: تم الحصول على العينات من بطانه الرحم بواسطه التوسيع والكحت في 95 (65.06%) من العينات وعن طريق ازاله الرحم في 46 (31.50 %) واستئصال السليله فى 5 (4.44%) من المرضى. شكلت الافات الحميده نسبه 71.9% وكانت سليلات بطانه الرحم اكثرها تكرارا 19.9% بينما شكلت الاورام الخبيثه 15.8%، 12.3% من العينات كانت غير كافية للتفسير. وجد فرط التنسج الغير لانمطي فى بطانه الرحم فى 17.8 % من العينات84.62% منهم هى فرط تنسج بسيط و 15.38 % هى فرط تنسج مركب. تم تشخيص سرطان بطانه الرحم فى 15.8 % من العينات . وكان الورم البطانانى الرحمى الغدى السرطانى اكثر الانواع النسيجيه شيوعا بنسبه 73.9 %، 41.2 % منهم هى اورام غديه سرطانيه ضعيفه التفاضل، بطانه الرحم

التكاثرى وبطانة الرحم الضموري والتهاب بطانه الرحم المزمن وجدت بنسبه 11 % و7.5% و 4.8 %على التوالى .

التضمين: غالبيه التغيرات المرضيه فى الانسجه فى نزف ما بعد الاياس هى افات حميده 71.9%. سليلات بطانه الرحم هى اكثر الانواع النسجيه سياده ونسبه خطر سرطان بطانه الرحم في نزف ما بعد الاياس هى 15.8 %.

INTRODUCTION AND LITERATURE REVIEW

Introduction to menopause:

Menopause is a universal and irreversible part of the overall aging process involving a woman's reproductive system, after which she no longer menstruates. Climacteric is the general term for the time from the period of this transition to the early postmenopausal phase of a woman's reproductive life cycle.[1]

Epidemiology:

The increasing number of middle-aged and older individuals includes a concomitant and continuing rise in the number of women who live most of their lives in a hypoestrogenic state. More and more women can expect to live approximately 79 years and to experience the consequences of gonadal hormone loss. The actual age of menopause, approximately 50-51 years, with the symptomatic transition to menopause usually commencing at approximately age 45.5 - 47.5 years.[1,2] Factors that lower the age of physiologic menopause include smoking,[2] hysterectomy, Fragile X carrier, autoimmune disorders, living at high altitude, or history of certain chemotherapy medications and/or radiation treatment.

Physiology of menopause:

Menopause results from loss of ovarian sensitivity to gonadotropin stimulation, which is directly related to follicular decline and dysfunction.

The oocytes in the ovaries undergo atresia throughout a woman's life cycle, and both the quantity and quality of follicles undergo a critical decline approximately 20-25 years after menarche. Thus, the variable menstrual cycle length during perimenopause can be due to anovulation or to irregular maturation of follicles. A shorter menstrual cycle length is the most common change that occurs during the perimenopausal period in women who have no pelvic pathology and who continue to ovulate.[3] The follicular phase of the menstrual cycle shortens because of the decreased number of functional follicles. Because these follicles, which are stimulated by follicle-stimulating hormone (FSH) during the first part of the menstrual cycle, have declined in number, less recruitment of oocytes occurs and the follicular phase shortens accordingly. Over time, as aging follicles become more resistant to gonadotropin stimulation, circulating FSH and luteinizing hormone (LH) levels increase. Elevated FSH and LH levels lead to stromal stimulation of the ovary, with a resultant increase in estrone levels and a decrease in estradiol levels. Inhibin levels also drop during this time because of the negative feedback of elevated FSH levels.[4] With the commencement of menopause and a loss of functioning follicles, the most significant change in the hormonal profile is the dramatic decrease in circulating estrogen levels. Without a follicular source, the larger proportion of postmenopausal estrogen is derived from ovarian stromal and adrenal secretion of androstenedione, which is aromatized to estrone in the

peripheral circulation.[5] With cessation of ovulation, estrogen production by the aromatization of androgens in the ovarian stroma and production in extragonadal sites continue, unopposed by progesterone production by a corpus luteum. Perimenopausal and menopausal women are thus often exposed to unopposed estrogen for long periods, which can lead to endometrial hyperplasia, a precursor of endometrial cancer. Estradiol levels decrease significantly because of loss of follicular production with menopause and postmenopause, but estrone, which is aromatized from androstenedione from nonfollicular sources, is still produced and is the major source of circulating estrogen in the postmenopausal female.[1] The clinical indication that menopause has occurred is the measure of an elevated FSH level. The FSH level rises more than the LH level because of the reduced renal clearance of FSH compared with LH. A slightly elevated or borderline menopausal FSH level in a perimenopausal woman may not be a reliable indicator of menopause because of the wide variation of FSH and LH levels in response to increased release of gonadotropin-releasing hormone (GnRH) by the hypothalamus and increased pituitary sensitivity to GnRH. Measuring FSH and LH levels again in the perimenopausal patient after 2-3 months is helpful in establishing whether the woman is progressing through menopause.[1]

Clinical effects of menopause:

Throughout the time when the physiologic changes in responsiveness to gonadotropins and their secretions occur, with resultant wide variation in hormonal levels, women often experience several symptoms that are collectively termed the climacteric syndrome. Typical climacteric symptoms include hot flashes or flushes, insomnia, weight gain, mood changes, irregular menses, and headache. As already noted, the length of time over which the climacteric occurs is widely variable; symptoms may begin during perimenopause and continue for 5-10 years after menopause. Irregular ovarian function and considerable estrogen level fluctuation not a deficiency of estrogen cause climacteric symptoms during menopause .Cessation of menstruation in women of the appropriate age continues to be the best confirmation of loss of follicular function as post menopause years progress with an accompanying loss of ovarian response to gonadotrophins. Associated symptoms of the climacteric also decline.[(1)]

The effects of gonadal hormone depletion can be obvious on pelvic examination. With loss of estrogen, the vaginal epithelium becomes redder because of thinning of the epithelial layer and increased visibility of the small capillaries below the surface. Later, as the vaginal epithelium further atrophies, the surface becomes pale because of a reduced number of capillaries. Rugation also diminishes, and the vaginal wall becomes smooth. Inside the pelvis, the uterus becomes smaller. Fibroids, if present,

become less symptomatic. Endometriosis and adenomyosis are also alleviated with the onset of menopause, and many patients with pelvic pain finally achieve permanent pain relief.

The menopausal ovary diminishes in size and is no longer palpable during gynecologic examination. A palpable ovary on pelvic examination warrants a full evaluation in all women who are menopausal or postmenopausal.[5]

Osteoporosis and menopause:

With the onset of menopause, BMD is rapidly lost because bone resorption, uncoupled with bone formation, is accelerated, where as formation continues at the premenopausal rate. Trabecular bone is affected more than cortical bone, and bone loss is therefore more commonly observed at vertebral and radial sites. Normal bone loss associated with senescence is different from the accelerated bone loss observed after menopause. Bone loss in the few years after onset of menopause may be as high as 20% of lifetime bone loss. Osteoclasts have been shown to have estrogen receptors, and these are hypothesized to be the mechanism by which estrogen replacement protects against osteoporosis.[5]Estrogen therapy (ET) is still considered a good therapy for osteoporosis, Postmenopausal women and elderly women should be treated early and on a long-term basis unless estrogen therapy is contraindicated.[6]

Cardiovascular issues and menopause:

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in men and postmenopausal women. Menopause increases the risk for women still further, independent of age. Prior to menopause, the risk of CAD for women lags behind the risk for men by approximately 10 years. After menopause, women come to have similar risks of CAD as men of the same age.[7] Initiating hormone therapy or estrogen therapy in the immediate peri or postmenopausal time is believed to be beneficial because significant atherosclerotic changes have not yet occurred. The benefit of estrogen on cardiovascular mortality rates is due to many factors. One mechanism appears to be estrogen effects on lipid metabolism, which includes reducing low-density lipoprotein (LDL) and increasing high density lipoprotein (HDL).[8]

Breast cancer and menopause:

Estrogen therapy is known to benefit postmenopausal women in a multitude of ways, mostly through the relief of vasomotor symptoms associated with the postmenopausal time. Estrogen is also beneficial for the prevention and treatment of osteoporosis. Much controversy exists about the use of estrogen and breast cancer. Some studies show an increased risk of breast cancer with postmenopausal estrogen use, whereas others show a decrease. Estrogen's possible link to cancer is also suggested by the fact that the risk of breast cancer is increased in women with an earlier age at

menarche and a later age at menopause. Currently, no woman with a strong family or personal history of breast cancer should be given hormone therapy or estrogen therapy.[9] The risk appears to be related to duration of use, with longer-term users being more affected. Women with a history of using hormone therapy have more localized tumors as well as better survival rates. That is, women receiving hormone therapy who are diagnosed with breast cancer are found to have more favorable staging at the time of diagnosis , including smaller tumor size, negative lymph node involvement, and well-differentiated tumor histology.[10]

Central nervous system and menopause:

The association of estrogen and memory function is an intriguing area of research. Normal aging itself induces a decline in certain cognitive capabilities, and a lack of estrogen may contribute to this process. The estrogen effect is one of slowing the decline of preserved memory function.[11]

Menopause markers:

Gonadotropin secretion increases dramatically after menopause. FSH levels are higher than LH levels, and both rise to even higher levels than in the surge during the menstrual cycle. The FSH rise precedes that of LH. Endometrial biopsy can show a range of histological appearances, from mildly proliferate to atrophic. No secretory changes are observed after menopause because no ovulation occurs, and therefore, no corpus luteum

forms to produce progesterone. Endometrial hyperplasia is a sign of hyperstimulation by estrogen from either endogenous sources or replacement therapy and may be a precursor of endometrial cancer.[1,3]

Replacement therapy and menopause:

The main reasons to treat symptoms of estrogen level fluctuation prior to actual menopause are to provide relief of vasomotor symptoms, avoid irregularity of menstrual cycle and preserve bone.

The time to begin therapy depends on the patient's current illness or illnesses, if any, and medical history. Whether a woman is perimenopausal or postmenopausal helps in choosing the most suitable type of therapy.

Contraindications to estrogen therapy are undiagnosed vaginal bleeding, severe liver disease, venous thrombosis, and personal history of breast cancer.[11]

Definition:

Post menopausal bleeding: abnormal uterine bleeding that occurs at least one year after menopause has been established.[12]

Causes of abnormal uterine bleeding in postmenopausal years:

1. Atrophy 25%.
2. Organic lesion: hyperplasia 16%.
3. Endometrial polyp 2-24%.
4. Endometrial carcinoma10%.
5. Exogenous hormones:

a. Oestrogen replacement.

b. Progestin therapy e.g. therapy of breast cancer.

6. Uncommon causes:

a. Endometritis.

b. Clotting disorders.

Investigation of PMB:

- History including duration and severity of bleeding, initiating factors such as intercourse or trauma.
- History of risk factor for hyperplasia and adenocarinoma including anovulation, obesity, hypertension and diabetes.[12]
- Medication HRT, topical estrogen,tamoxifen.
- PAP smear.
- Family history of gynecological cancer.
- Gynecological history.
- Obstetric history.

Clinical examination:

Abdominal, bimanual examination, speculum examination of the vagina and cervix. The clinical-gynecological investigation should prove the source of postmenopausal bleeding according to the anatomical site-uterine, infra-, or suprauterine. The causes of infrauterine bleeding may

easily be diagnosed by means of inspection of the external genitalia and further by using a speculum.

Cytology and colposcopy:

Cytology and colposcopy supported by bimanual examination, exclude cervical carcinoma as a cause of bleeding. Both adnexa should always be investigated and the findings sonographically documented, so that solid cystic masses in the adnexal area can be better identified as suprauterine causes of postmenopausal bleeding. Then the uterus should be investigated. The causes of uterine bleeding are of major importance. Atypical endometrial cells on the cytological smear arouse suspicion of endometrial carcinoma.[13]

Transvaginal sonography (TVS):

TVS is used as a first step in the diagnostic workup and is preferred over uniform biopsy of postmenopausal women with vaginal bleeding as (1) it is a less invasive procedure than endometrial biopsy, (2) is generally painless, (3) has no complications, and (4) may be more sensitive for detecting carcinoma than blind biopsy. A limitation of ultrasound is that an abnormal finding is not specific: ultrasound cannot always reliably distinguish between benign proliferation, hyperplasia, polyps, and cancer.[13]

Hydroultrasonography (Transvaginal ultrasound with SIS):

This is accomplished by placing a small volume of saline into the endometrial cavity and then repeating the vaginal ultrasonogram.

In many instances in which the original vaginal ultrasonogram shows significant endometrial thickness, an ultrasonogram can help differentiate other pathology from true endometrial thickness.

Hysteroscopy is necessary in postmenopausal women with an endometrium of 4 mm or more, as well as in premenopausal patients with endometrial thickness more than 5 mm and in those with suspected polyps or myomas. In postmenopausal women without vaginal bleeding, the risk of cancer is approximately 6.7% if the endometrium is thick (> 11 mm) and 0.002% if the endometrium is thin (< or = 11 mm).[14]

Endometrial biopsy:

Indication for endometrial biopsy or curettage:

1. Determination of the cause of the abnormal uterine bleeding
2. Assessment of the response of the endometrium to hormonal therapy especially estrogen replacement in perimenopausal and postmenopausal women.
3. Evaluation the status of the endometrium in infertile patients including histologic dating
4. Evacuation of products of conception.[15]

5. Presence of atypical or abnormal glandular cells in a cervical-vaginal cytologic sample that requires endometrial sampling to exclude hyperplasia or carcinoma.[12]
6. Endometrial sampling prior to hysterectomy to exclude significant pathology, although this procedure yields little pathology in the absence of history of abnormal uterine bleeding.[16]

Procedure:

Although fractional dilatation and curettage was historically the definitive diagnostic procedure to help rule out endometrial cancer, in current practice endometrial biopsy as an office procedure is quick, well tolerated, and quite sensitive for making the diagnosis.

If endometrial pathology is not present on biopsy specimens and the patient has no further bleeding, no additional diagnostic tests need to be performed. If the patient continues to be symptomatic, then further evaluation of the endometrial cavity is necessary.

Hysteroscopically directed biopsy: Another diagnostic procedure that has been advocated by some as an even more accurate way of determining the status of the endometrium.

Dilatation and curettage: The current role of the formal dilatation and curettage is probably very limited because the diagnosis can usually be made in the office.

Endometrial hyperplasia is a non physiologic non invasive proliferation of the endometrium that results in morphologic patterns of glands with irregular shapes and varying size. This disorder results from sustained un opposed oestrogen stimulation and presents clinically as abnormal uterine bleeding. Hyperplasia occurs most frequently in perimenopausal women since they frequently have anovulatory cycle, but also occurs in postmenopausal women who either have excess endogenous oestrogen level or are receiving exogenous oestrogen (18).Hyperplasia may arise on occasion in young women including teen agers, since sporadic anovulation occurs in the reproductive ages and anovulatory cycles are frequent in adolescents.[19]

World Health Organization (WHO) classification of endometrial hyperplasia:

This system characterizes the glandular architectural pattern as simple or complex and describes the presence or absence of nuclear atypia.

Hyperplasia (without atypia):

a. Simple hyperplasia: Increased number of glands but regular glandular architecture.

b. Complex hyperplasia - Crowded irregular glands.

2. Atypical hyperplasia:

a. Simple hyperplasia with atypia: Simple hyperplasia with presence of cytologic atypia (prominent nucleoli and nuclear pleomorphism)

b. Complex hyperplasia with atypia: Complex hyperplasia with cytologic atypia.

Simple hyperplasia was associated with a 1% rate of progression to cancer, 3% rate of progression to complex hyperplasia, and 8% rate of progression to simple atypical hyperplasia, whereas complex atypical hyperplasia had a 29% rate of progression to cancer.[20]

Not only does the concern exist for atypical hyperplasia progressing to invasive cancer, but numerous studies found concurrent carcinoma at rates ranging from 17-52%.[21] Part of the difficulty in diagnosing concurrent carcinoma is due to lack of reproducibility in diagnosing hyperplasia, especially atypical hyperplasia versus carcinoma among even expert gynecologic pathologists.[22]

Pathophysiology:

Endometrial hyperplasia results from continuous estrogen stimulation that is unopposed by progesterone. This can be due to endogenous estrogen or exogenous estrogenic sources. Endogenous estrogen may be caused by chronic anovulation associated with polycystic ovary syndrome (PCOS) or perimenopause. Obesity also contributes to

unopposed estrogen exposure due to chronic high levels of estradiol that result from aromatization of androgens in adipose tissue and conversion of androstenedione to estrone. Endometrial hyperplasia and cancer can also result from estradiol-secreting ovarian tumors such as granulosa cell tumors.[20]

Exogenous estrogen without progesterone has been associated with increased endometrial hyperplasia and adenocarcinoma. The Postmenopausal Estrogen/Progestin Interventions(PEPI) trial found that unopposed estrogen exposure with 0.625 mg of conjugated equine estrogens increased the risk of complex hyperplasia by 22.7% and atypical hyperplasia by 11.8% over 3 years of use compared with a less than 1% increase in placebo controls[24]. Tamoxifen, with its estrogenic effect on the endometrium, increases the risk of endometrial hyperplasia and endometrial cancer. The risk of progression to cancer is associated with an increased duration of use[25].

The exact mechanism of estrogen's role in the transformation of normal endometrium to hyperplasia and cancer is unknown. Genetic alterations are known to be associated with hyperplasia and type I endometrial cancers. Lesions with hyperplasia are associated with microsatellite instability and defects in DNA mismatch repair genes. *PTEN* tumor suppressor gene mutations have also been found in 55% of

hyperplasia cases and 83% of hyperplasia cases once it has progressed to endometrial cancer.[26]

Mortality/Morbidity:

Endometrial carcinoma is the most common gynecologic malignancy and the fourth most common cancer in women, significant morbidity or mortality can occur if endometrial hyperplasia is untreated or concurrent malignancy is present.

Endometrial hyperplasia is often associated with irregular or heavy vaginal bleeding, which can lead to disruptions with quality of life. Occasionally, uterine hemorrhage occurs, which may necessitate medical or surgical interventions, and blood transfusion therapy.

Age:

Endometrial hyperplasia is most frequently diagnosed in postmenopausal women, but women of any age can be at risk if they are exposed to a source of unopposed estrogen. Endometrial hyperplasia can frequently be seen in young women with chronic anovulation.

Clinical features:

Other risk factors for endometrial hyperplasia are the same as those for endometrial adenocarcinoma, including obesity, nulliparity, early menarche, and late menopause. While unopposed estrogen in oral contraceptive pills or estrogen replacement therapy increases the risk of hyperplasia and cancer, combination oral contraceptive pills and

combination hormone replacement therapy does not increase and may decrease the risk of hyperplasia and cancer.[20]

The most common clinical presentation of patients with endometrial hyperplasia is abnormal uterine bleeding, whether in the form of menorrhagia, metrorrhagia, or postmenopausal bleeding. Others present with abnormal vaginal discharge or Pap smear results showing glandular abnormalities.

Diagnosis of endometrial hyperplasia is usually made by sampling the endometrial cavity. Tissue sampling should be performed in women with risk factors who present with symptoms of abnormal vaginal bleeding or discharge. This includes women older than 40 years with abnormal bleeding, younger than 40 years with bleeding and risk factors, with persistent bleeding, and with unopposed estrogen replacement therapy. In addition, a biopsy should be performed in women with AGUS (atypical glandular cells of undetermined significance) Pap smear or endometrial cells in Pap smears of women older than 40 years.[27] While no evidence of improved survival has been documented, some also advocate routine screening by endometrial biopsy in asymptomatic women with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome or those on tamoxifen therapy.

Treatment:

Once a tissue diagnosis of endometrial hyperplasia is made, treatment depends on the patient's symptoms such as the degree of bleeding, presence of cytologic atypia and patient's surgical risks. Progestins can effectively treat endometrial hyperplasia, and they can serve as preventiors of recurrence in those with continued risk factors. Hyperplasia without atypia responds well to progestins. More than 98% of women with hyperplasia treated with cyclic progestins experienced regression of the disease in 3-6 months. The PEPI trial showed a 94% normalization of complex or atypical hyperplasia in 45 women treated with progestins.Multiple regimens of progestin therapy have been found effective in reversing hyperplasia.[28]

If hyperplasia with atypia is found on dilatation and curettag) or endometrial biopsy, definitive treatment with hysterectomy is recommended due to the high rate of concurrent endometrial cancer. However, if the patient is not a surgical candidate, then concurrent cancer must first be ruled out by D & C with hysteroscopy prior to medical management. . Biopsy is recommended after 3 months to check for response to medical therapy, and continued surveillance after regression of the lesion is recommended every 6-12 months if risk factors persist.[29]

Endometrial adenocarcinoma: is the most common malignant tumor of the female genital tract. This neoplasm represents a biologically

and morphologically diverse tumor with different pathogenesis.[30] The typical endometrial adenocarcinoma is well to moderately differentiated with or without squamous differentiation and accounts for 80-85% of all endometrial adenocarinoma.The typical patient is perimenopausal or postmenopausal obese ,hypertensive and diabetic. The low grade tumors are frequently associated with atypical hyperplasias that result from unopposed estrogenic stimulation. The prognosis is generally good, with a 5 years survival of 80% or better.The high grade carcinoma appears to be less related to sustained estrogen stimulation.[30] These tumors account for10-15% of all endometrial carcinomas and include histologic subtypes such as clear and serous carcinomas along with other carcinomas that show high grade nuclear features. The tumors tend to occur in older post menopausal women. They usually invade the myometrium deeply, permeate lymphatic and vascular channels, and may show extrauterine spread at the time of hysterectomy.[12]

Age:

Endometrial adenocarcinoma occurs during the reproductive and menopausal years. The median age of women with this malignancy is early in the seventh decade of life, although most patients are aged 50-59 years. Approximately 5% of women younger than 40 years have adenocarcinoma, and 20-25% of women are diagnosed before menopause.[12]

Causes:

Multiple epidemiological risk factors have been identified in patients who have adenocarcinoma of the endometrium.

a. Endogenous factors: Nulliparity also increases risk 2- to 3-fold compared with parity. An individual who has had a late menopause (aged >52 y) also appears to have an increased risk.

b. Unopposed estrogen: Unopposed estrogen, either as replacement therapy or endogenously produced (e.g., granulosa cell tumor, polycystic ovarian disease), increases the risk of endometrial cancer several times.

c. Obesity is known to increase endogenous estrogen because the presence of fat appears to be responsible for the conversion of androstenedione to estrogen compounds at a much higher rate than if fat is not present. Anovulation which may be secondary to unopposed estrogen also appears to contribute to this situation.[31]

Tamoxifen The most widely used anticancer drug is tamoxifen, and this drug has been suggested by some studies to cause an increased incidence of adenocarcinoma of the endometrium. These data were derived from retrospective analyses in which adenocarcinoma of the endometrium was not an end point in multiple prospective randomized studies evaluating the role of tamoxifen in patients with breast cancer. In contrast to tamoxifen, increasing data indicate that the use of combination oral

contraceptives (OCs) decreases the risk of developing endometrial cancer (32). Several studies have noted that women who use OCs at some time have a 0.5 relative risk of developing endometrial cancer compared with women who have never used OCs.

Associated medical conditions:

Some associated medical conditions have been found to increase the incidence of endometrial cancer.

Breast, ovarian.and colon .cancers are frequently observed in women with endometrial cancer. Data suggest that women who have had breast cancer have a 2- to 3-fold increased risk of subsequently developing endometrial cancer. Women who have hereditary nonpolyposis colon cancer (HNPCC) appear to have a markedly increased risk for developing endometrial cancer. Women with HNPCC account for only 2-10% of all female cases of colon cancer, but approximately 5% of all endometrial cancers occur in women with this risk factor. These women have a 22-50% lifetime risk of developing endometrial cancer, and the disease tends to occur at a younger age (approximately 15 years earlier). The greatest risk of developing endometrial cancer in women with HNPCC occurs from age 40-60 years, at which time the absolute risk is greater than 1% per year.

f. Family history:

Individuals with a family history of endometrial cancer appear to be at increased risk.[(32)]

Pathogenesis of endometrial adenocarcinoma:

Endometrial adenocarcinomas that are associated with hyperplasia and the aforementioned risk factors tend either to be well differentiated mimicking normal endometrial glands (endometrioid) in histologic appearance,or to display altered differentiation (mucinous,tubal,squmaous differentiation). This group of tumours is associated with a more favourable prognosis than tumours without hyperplasia .Although endometrial carcinomas may be associated with separate primary neoplasm arising in ovarian endometriosis; they tend not to spread to peritoneal surface.[30]

Endometrioid adenocarcinoma is closely linked to prolonged estrogenic stimulation of the endometrium.In addition to treatment with exogenous oestrogen, obesity diabetes, nullparity, early menarche and late menopause. Each risk factor points to relative hyperestrinisim, Women with ovarian a genesis do not develop endometrial cancer unless treated with exogenous oestrogen

Nonendometrioid cancer especially serous and clear cell adenocarcinoma,are unrelated to oestrogen exposure and usually occurs in women in their 60s and 70s . The adjacent endometrium is usually atrophic, a sign of oestrogen deficiency.

Occasionally, the tumour may show a precursor form, term endometrial intraepithelial neaplasia.

Endometrial cancer also occurs in association with a higher incidence of both breast and ovarian cancer in closely related women suggesting a genetic predisposition.Moreover, it is the most common extra colonic cancer in women with the hereditary nonpolyposis syndrome (Lynsch syndromeII), which is also associated with breast and ovarian cancers.[34]

WHO classification of endometrial adenocarcinoma:[35]

- Endometrioid adenocarcinoma (NOS)
- Variants:
    - Ciliated
    - secretory
- Adenocarcinoma, NOS, with squamous differentiation.
- Mucinous adenocarcinoma.
- Secretary adenocarcinoma.
- Clear adenocarcinoma.
- Squamous adenocarcinma.
- Undifferentiated carcinoma.
- Mixed carcinoma.
- Metastatic carcinoma.

Endometrioid adenocarcinoma (NOS):

This type of endometrial cancer is composed entirely of glandular cells and it is the most common histologic variants. Many examples of

endometrial adenocarcinoma have the typical, usual or (not other wise specified) pattern referred to as endometrioid carcinoma. More than one half of all endometrial carcinomas have this typical endometrioid pattern from 20-30% of endometrial carcinomas shown an endometrioid pattern with squamous differentiation. Previously these tumours with squamous differentiation were separated into two categories: adenoacanthoma denoted tumour that had a cytologically benign-appearing squamous epithelium (squamous metaplasia), and adenosquamous carcinoma denoted tumour that had a cytologically malignant appearing component. More recently, studies have shown that endometrioid carcinomas with or without squamous differentiation behave in the same fashion when stratified according to the grade of the glandular components .Accordingly, these tumours are best classified as adenocarcinomas with squamous differentiation and graded. The terms adenoacanthoma and adenosquamous carcinoma are no longer used for endometrial carcinomas.[12]

Serous adenocarcinoma:

Histologically resembles serous adenocarcinoma of the ovary. It also behaves more like ovarian carcinomas than endometrial tumours, often showing transcoelomic spread (34).This tumour arises within atrophic endometrium from a precursor known as endometrial intraepithelial carcinoma (EIC).[33]

Clear cell adenocarcinoma:

It is a tumour of elderly women, It is composed of large cells with copious cytoplasmic glycogen (clear cell) or of cells with bulbous nuclei that line glandular lumina (hobnail cells). Clear cell and serous carcinoma are poorly differentiated adenocarcioma with poor prognosis.

Secretory carcinoma:

Describes cells with subnuclear vacuolization, usually in premenopausal women, the tumour is well differentiated. Secretory carcinoma has the most favourable outcome of any adenocarcinoma, presumably because the cells are well differentiated.

Grading of endometrial carcinoma:

Grade1: well differentiated adenocarcinoma (95% of the tumour forms glands.

Grade 2: differentiated carcinoma with partly solid areas (<50%).

Grade 3: predominantly solid or entirely undifferentiated (>50% of the tumour has a solid growth pattern).

Serous and clear cell carcinoma is grade 3 tumour.

International Federation of Gynaecology and Obstetrics (FIGO) staging of corpus cancer:

Stage	**Description**
Ia G123:	Tumour limited to the endometrium
I b G123	Invasion of less than half of the myometrium

IcG123	Invasion of more than half of the myometruim
IIaG123	Endocervical glandular involvement only
IIb G123	Cervical stromal invasion
IIIaG123	Tumour invades serosa and or adnexae and or positive peritoneal cytology
IIIb G123	Vaginal metastases
IIIc G123	Metastases to pelvic and or paraaortic lymph nodes
IVa G123	Tumour invasion of bladder and or bowel mucosa
IVb	Distant metastases including intraabdominal and or inguinal lymph nodes

Staging of endometrial cancer employed a variety of histologic risk factors including grade, depth of myometrial invasion, involvement of the cervix and peritoneal cytology.[35]

Management:

Women with well differentiated cancer confined to the endometrium are usually treated by simple hysterectomy alone or in combination with radiation giving about90% 5years survival in stageI(grade 1 or2)disease. This rate drops to75% for grade 3stage I disease and to 50% or less for stage II and III endometrial carcinoma.[30] Postoperative radiation is administered if (1) the tumour is poorly differentiated (2) the myometrium is more than superficially involved. (3) The cervix is involved (4) the lymph nodes contain metastases.[34]

Prognosis:

Survival in endometrial carcinoma is related to multiple factors including (1) the stage and histologic grade and type, (2) age, (3) progesterone receptor activity, (4) depth of myometrial invasion, (5) other measurable risk factors such as extent of lymphovascular invasion and results of peritoneal washings. The actual survival rate of all patients with endometrial carcinoma following treatment is 80% after the second year decreasing to65% after 10 years.[34]

Uterine papillary serous and clear cell carcinoma have propensity for extrauterine (lymphatic or transtubal) spread, even when confined to the endometrium or its surface epithelium <50% of patients with these tumours are alive 3 years after diagnosis and 35% after 5 years.[30]

Endometrial polyps:

Definition:

A polyp is a benign overgrowth in the endometrial cavity. Polyps occur over a wide age range but is most common in the fourth and fifth decades, becoming less frequent after the age of 60.[12]

Pathogenesis:

Polyps are thought to arise from endometrial foci that are hypersensitive to estrogenic stimulation or unresponsive to progesterone. In

either case, such foci don’t slough during menstruation and continue to grow.[34]

Pathology:

Most endometrial polyps arise in the fundus, although they may originate in any location within the endometrial cavity. They vary from several millimetres in length to a growth filling the entire endometrial cavity, most are solitary, but 20% are multiple.[34]

Classification and histologic features:

Classification of endometrial polyps:

- Hyperplastic.
- Atrophic.
- Functional.
- Adenomymatous.
- Mixed endometrial-endocervical.
- A typical polypoid adenomyoma.

This classification has little clinical significance but is useful for correct identification of these lesions and separating them from hyperplasia.[12]

Despite their diverse growth patterns, all polyps show several histologic features that facilitate their diagnosis. One important feature of polyps is the presence of large, polypoid tissue fragments, these fragments tend to be lined on three sides by surface epithelium. Often much smaller

fragments of normal endometrium are admixed with the large fragments of a polyp.

Polyps commonly show dense stroma. In addition they frequently contain thick walled blood vessels especially when they become large. Small veins in the superficial stroma become ectatic. The glands in polyps are irregular in shape and have a highly variable architecture. In addition to these characteristic features, a polyp may show evidence of focal glandular and stromal break down, usually due to thrombosis of superficial dilated veins.[37]

Hyperplastic polyps: Are most common, they are highly variable in size up to several centimetres in great dimension. Regardless of size, they show irregular proliferating glands with pseudo stratified nuclei and mitotic activity. The surface and glandular epithelium often show epithelial cytoplasmic changes. These include squamous, eosinophilic and ciliated cell changes.

Atrophic polyps: Also known as inactive polyps are usually seen in postmenopausal women. These polyps contain atrophic glands lined by low columnar epithelium showing no mitotic activity. The stroma appears dense and fibrotic.

Functional polyps: These polyps like the endometrium around them are hormonally responsive and show proliferative or secretory changes.

The stroma may show oedema or predecidual change but often is dense and in- active.

Mixed endometrial-endocervical polyps: Some polyps originate in the upper endocervix and lower uterine segment and show both endocervical and endometrial type of glands. These polyps tend to have a fibrous stroma resembling the stroma of the lower uterine segment.

Adenomymatous polyps: these polyps have smooth muscle in their stroma usually as irregular bundles and strands in proximity to thick walled vessels. Most often these are large polyps in which the stroma has undergone partial smooth muscle proliferation.[38,39]

Atypical polypoid adenomyoma: This is an unusual and distinctive polyp characterized by glands that are lined by a typical epithelium and surrounded by cellular smooth muscle.[40] It typically occurs in premenopausal or perimenopausal women with mean age of 40 years. A few cases have been associated with Turner syndrome and appear to be a complication of long term stimulation of the endometrium.[41]

Endometritis: Is usually a disorder of reproductive years although it may occur in postmenopausal patients. Endometrial inflammation typically accompanies PID of the upper genital tract. It may also be associated with a recent pregnancy either an abortion or term pregnancy. Other possible causes include instrumentation, such as prior biopsy or the presence of an organic lesion such as polyp, leiomyoma, hyperplasia or carcinoma.

Endometrial inflammation often is non specific and rarely has morphologic features that indicate a definite aetiology.

The non specific forms of endometritis have traditionally been separated in to acute and chronic forms depending on the type of inflammatory infiltrate, most are referred to as chronic non specific endometritis.

Acute endometrial inflammation is relatively infrequent except for puerperal related infection.[12]

Nonspecific endometritis: endometritis may be focal or diffuse and can range from a subtle inflammatory infiltrate to a pronounced inflammatory reaction, endometritis typically shows patterns of mixed inflammatory infiltrate containing plasma cells and lymphocytes and not infrequently neutrophils and eosinophils. The other morphologic changes include reactive stroma, epithelial changes, abnormal glandular development and evidence of glandular and stromal break down.[42]

Causes of chronic endometritis:

1. Granulomatous endometritis:

Granulomatous inflammation of the endometrium is in frequent, and often the process is due to mycobacterium tuberculosis, and infection usually indicates advance disease.

Tuberculous endometritis causes abnormal uterine bleeding in postmenopausal patients.[43]

2. Actinomycosis:

Infection by A. israeli is another rare cause of endometritis.The organism typically is found in endometritis associated with the use of intrauterine cervical device .The organisms show the typical sulphur granules morphology and can be stained by tissue gram stain (methen amine silver stain).[44]

3. Cytomegalovirus:

This occurs in immunosuppressed patients or it may be found in women with no known underlying disorders, regardless of the immunologic status. The issue shows the characteristic nuclear and cytoplasmic inclusions in the epithelial cells and occasional endothelial cells.[12]

4. Herpes virus:

Rarely infects the endometrium, but it may occur, usually as an ascending process associated with cervical infection. When present in the endometrium it can cause patchy necrosis of the glands and stroma .the diagnosis is established by identifying cells that show typical cytopathic effect. Type A inclusion and multinucleated cells with molded ground glass nuclei can be found in the glandular epithelium or the stroma in areas of necrosis.[12]

5. Chlamydia.trachomatis:

Infection is usually marked. The inflammatory infiltrate tends to be diffuse with plasma cells, lymphocytes, and lymphoid follicles with typical lymphocytes. The inflammatory response to Chlamydia also may be mixed with an infiltrate of acute as well as chronic inflammatory cells.Stromal necrosis and reactive atypia of the epithelium may be present.[45]

JUSTIFICATION

PMB is a common clinical problem in both general and hospital settings, representing 5% of all gynaecologic outpatients attendances. The incidence of spontaneously occurring PMB in the general population can be as high as 10% immediately after menopause.

PMB is the commonest symptom of carcinoma of the endometrium. Of postmenopausal women with vaginal bleeding, 10%-15% have endometrial carcinoma. Endometrial cancer is the most common malignancy of the female genital tract accounting for 7% of all invasive cancer of women excluding skin cancer. Unlike other malignancies, endometrial cancer often presents at an early stage when there is a possibility of curative treatment by hysterectomy. Survival decreases with increase staging and lower histological differentiation. Thus patients presenting with PMB should be worked up on priority basis to detect and mange carcinoma at an early stage.

OBJECTIVES

General objective:

To identify the histopathological patterns of postmenopausal bleeding in endometrial biopsies received in the National Health Laboratory in Khartoum in the years2009-June 2010

Specific objectives:

1. To identify the frequency and distribution of histopathological patterns of endometrial biopsies taken from women presenting with postmenopausal bleeding.
2. To estimate the risk of endometrial cancer in endometrial biopsies taken from women presenting with postmenopausal bleeding.

MATERIALS AND METHODS

Study design:

Retrospective (cross-sectional), descriptive study.

Study field:

Histopathology department/National health laboratory.

Study population:

The study included 146 tissue specimens taken from women presenting with postmenopausal bleeding.

Inclusion criteria:

All endometrial biopsies taken from women presenting with postmenopausal bleeding.

Exclusion criteria:

1. Failure to find paraffin block and or slides.
2. Endometrial biopsies taken from women presenting with vaginal bleeding during reproductive age.

Specimen collection and identification:

All issued reports from National health laboratory during the period from January 2009-june2010 were revised to obtain the lab numbers of all cases presented with postmenopausal bleeding. Tissue blocks and slides were collected, accordingly, slides were revised.

Materials and methods of identification:

Endometrial biopsies or hysterectomy specimens were fixed in formalin. Representative pieces of tissue were selected by a pathologist, processed by an automatic tissue processor, and then embedded in paraffin wax in form of blocks.

Sections average 4 microns in thickness were cut in a rotary microtome. Slides were prepared and stained with heamatoxylin and eosin (H&E).

For the purpose of this study slides were prepared from retrieved blocks and sections reexamined. The data were analyzed using computer program SPSS.

RESULTS

The age of women presenting with PMB in whom endometrial sampling was performed ranged from (45-90) years, with the highest frequency in (45-54) age group 59(40.4%) as shown in (Table 1).

Ninety five (65.06%) of endometrial biopsies were obtained by dilatation and curettage, 46(31.50%) by hysterectomy and 5(3.44%) by polypectomy (Figure 1).

Histopathological patterns of endometrial biopsies:

The majority of the lesions were benign 71.9% while malignant conditions constituted only (15.8%) as shown in (Figure 2).

Endometrial polyps were the predominant histologic pattern constituted 19.9%, 62.1% were hyperplastic, 27.6% were atrophic, functional polyps seen in 6.9% of biopsies, 3.4% were adenomyomatous (Tables 2 and 3).

Metaplastic change was diagnosed in38.9% of hyperplastic polyps, 57.1% displayed squamous metaplastic change, syncytial papillary change in 14.3% and ciliated metaplasia in 28.6% (Table 4, Figure 4).

Endometrial hyperplasia without atypia was diagnosed in 17.8% of biopsies, 84.62% were simple hyperplasia and 15.38% were complex hyperplasia (Figure 3).

Endometrial cancer constituted 15.8%, endometrial adenocarcinoma was the predominant endometrial cancer with a figure of (73.9%),

squamous carcinoma came second (17.4%), stromal sarcoma and serous cell carcinoma were both rare, constituting 4.3% for each. Most endometrial adenocarcinoma (41.2%) were poorly differentiated, well differentiated adenocarcinoma in 23.5% and 35.3% were moderately differentiated adenocarcinoma (Tables 5 and 6).

Proliferative endometrium was diagnosed in 11% of endometrial biopsies, atrophic endometrium in 7.5% and in active endometrium in 1.4% (Table 2).

Other patterns including hormonal effects, secretory endometrium and nondatable endometrium were diagnosed in 10% of biopsies, while, 12.3% of biopsies were inadequate for interpretation (Figure 2).

Table (1) Age distribution among the study population

Age (in years)	Frequency	Percentage
45-54	59	40.4
55-64	47	32.2
65-74	30	20.5
75-84	7	4.8
85-94	3	2.1
Total	**146**	**100.0**

Table (2) Distribution of histopathological patterns of the study population

Patterns	**Frequency**	**Percentage**
Proliferative endometrium	16	11.0
Inactive endometrium	2	1.4
Atrophic endometrium	11	7.5
Edometrial hyperplasia without atypia	26	17.8
Endometrial polyps	29	19.9
Malignancy	23	15.8
Chronic endometritis	7	4.8
Inadequate for interpretation	18	12.3
Prolifreative endometrium+hyperplastic polyps	2	1.4
Complex hyperplasia without atypia + hyperplastic polyp with ciliated change.	1	0.7
Simple hyperplasia+adenomyomatous polyps	1	0.7
Others	10	6.8
Total	**146**	**100.0**

Table (3) Histolgic subtypes of endometrial polyps

Type	Frequency	Percentage
Hyperplastic	18	62.1
Atrophic	8	27.6
Functional	2	6.9
Adenomyomatous	1	3.4
Total	**29**	**100.0**

Table (4) Distribution of metaplastic change in hyperplastic polyps

Metaplastic change	Frequency	Percentage
Yes	7	38.9
No	11	61.1
Total	**18**	**100.0**

Table (5) Histologic subtypes of endometrial cancer

Type	Frequency	Percentage
Adenocarcinoma	17	73.9
Squamous cell carcinoma	4	17.4
Stormal sarcoma	1	4.3
Serous carcinoma	1	4.3
Total	**23**	**100.0**

Table (6) Degree of differentiation of endometrial adenocarcinoma

Degree of differentiation	Frequency	Percentage
Well differentiated (grade I)	4	23.5
Moderate differentiated (grade II)	6	35.3
Poor differentiated (grade III)	7	41.2
Total	**17**	**100.0**

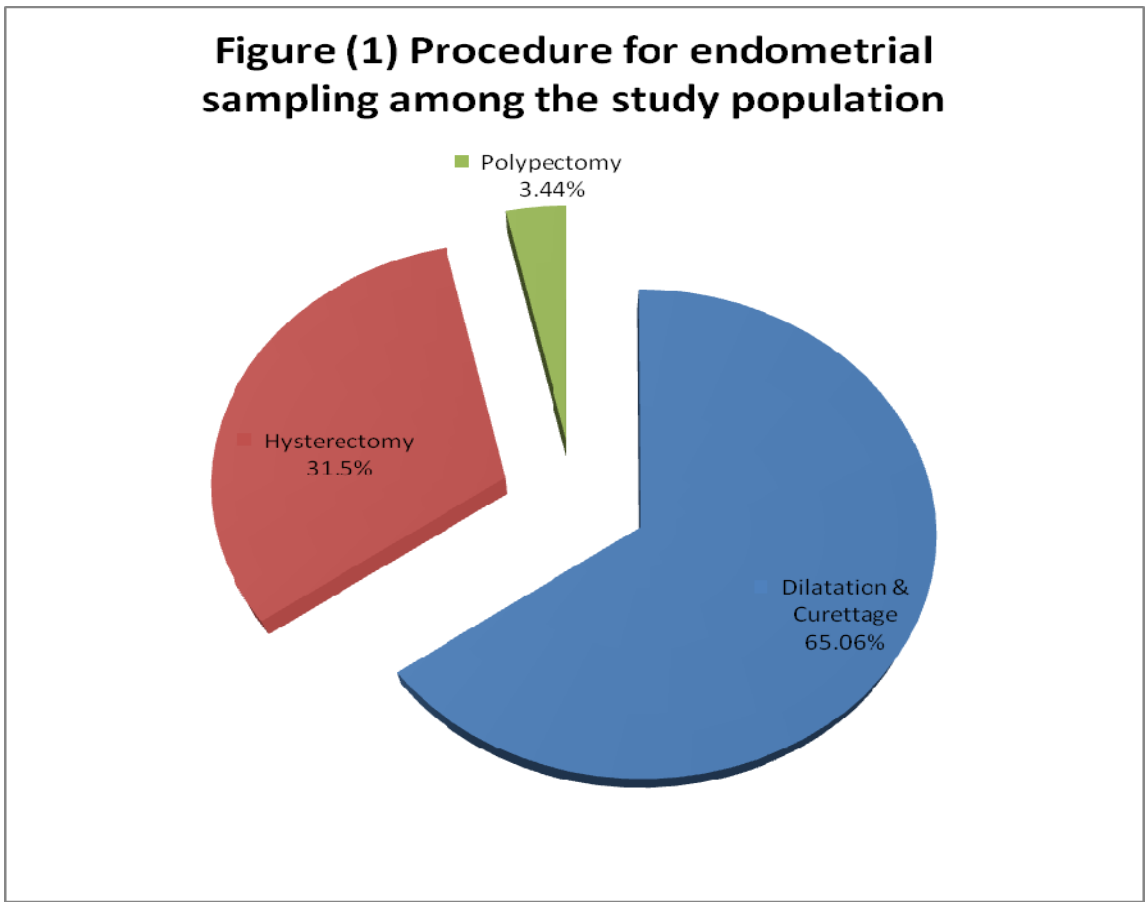


Figure (1) Procedure for endometrial sampling among the study population
Polypectomy 3.44%
Hysterectomy 31.5%
Dilatation & Curettage 65.06%

Figure (2) Distribution of histopathological patterns among the study population

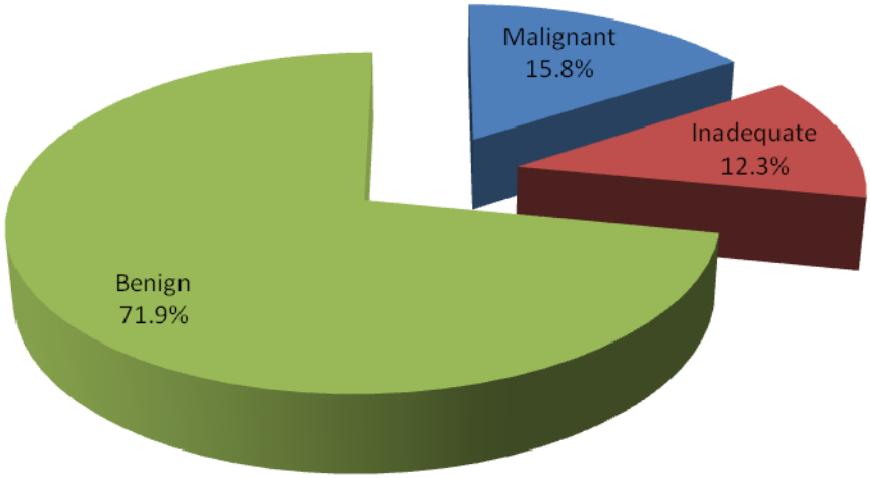


Figure (3) Types of endometrial hyperplasia (n = 26)

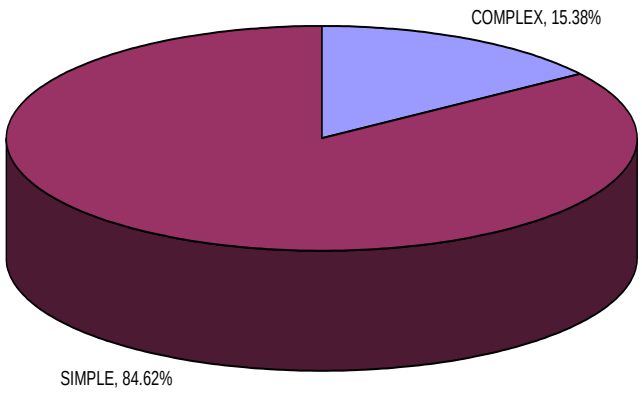


Figure (4) Distribution of metaplastic change in hyperplastic polyps (n = 7)

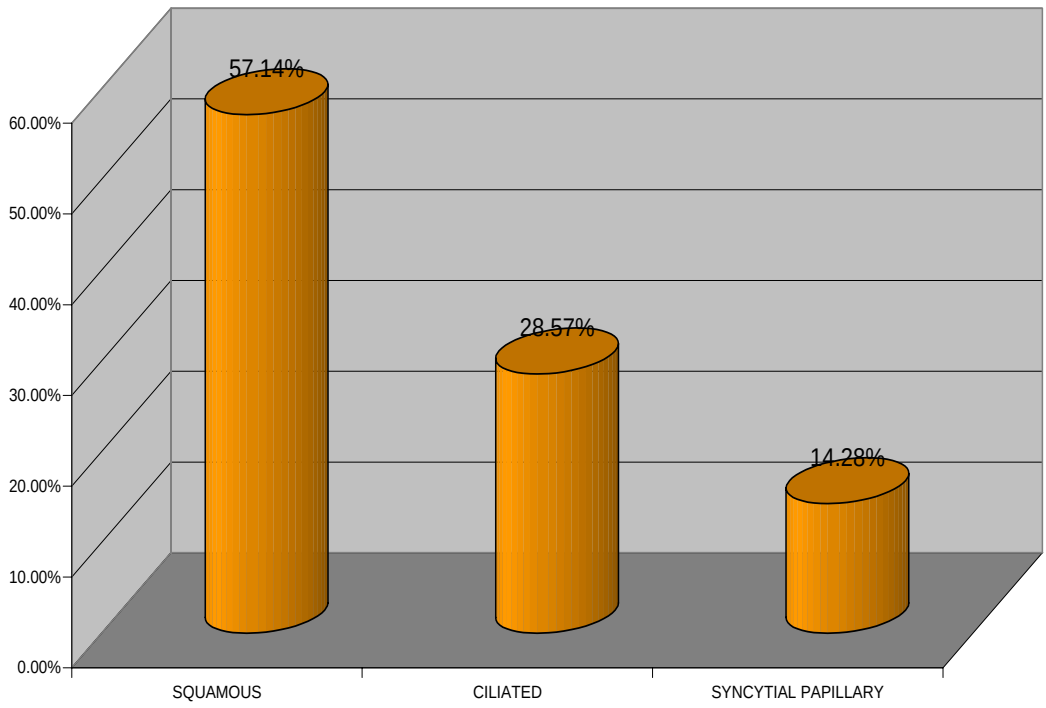
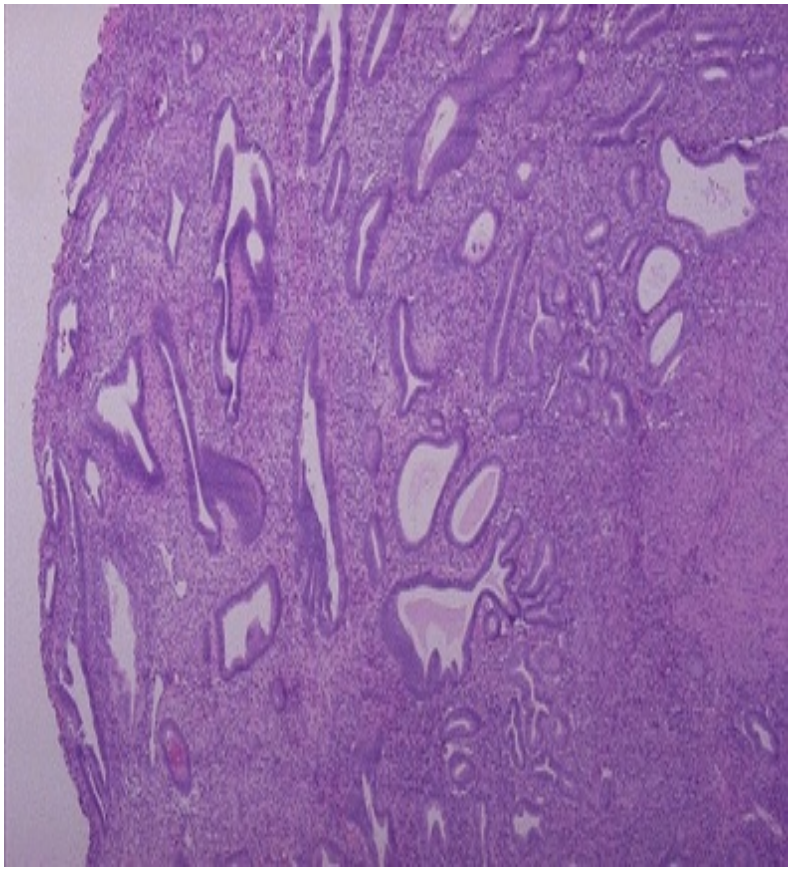
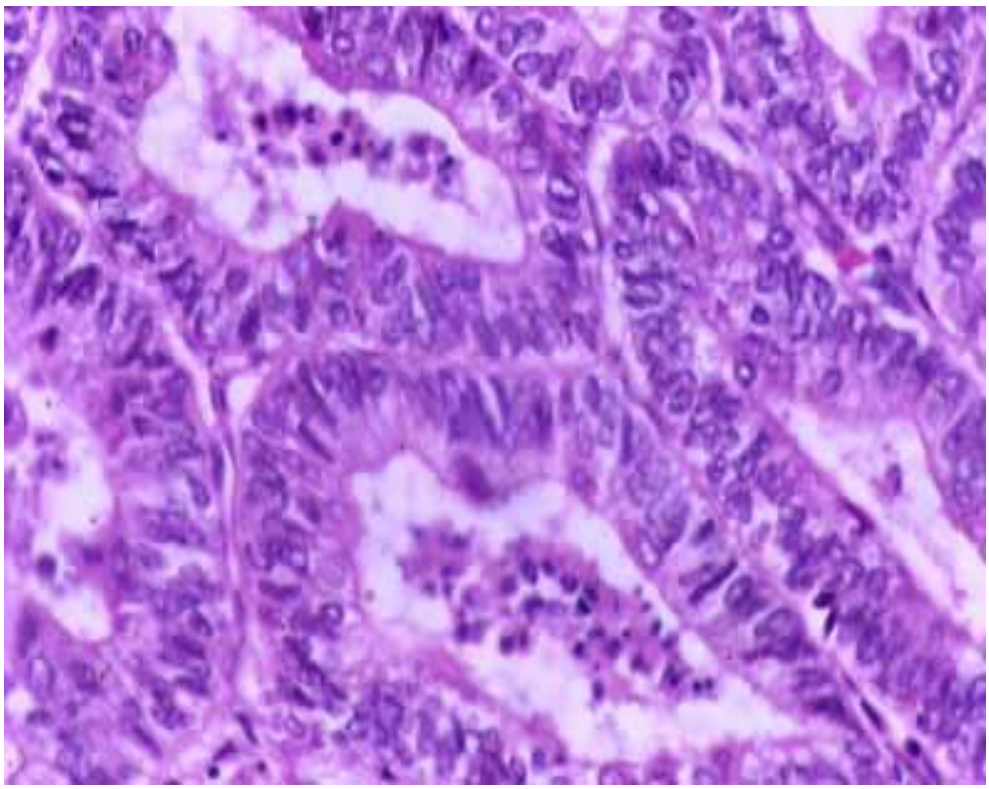


Figure (5) Simple Hyperplasia



Simple hyperplasia(cystic hyperplasia) glands are cystically dilated with occasional outpouching surrounded by abundant densely cellular stroma and give a (Swiss cheese appearance) .No cellular a typia is present(H&E,X10 objective).

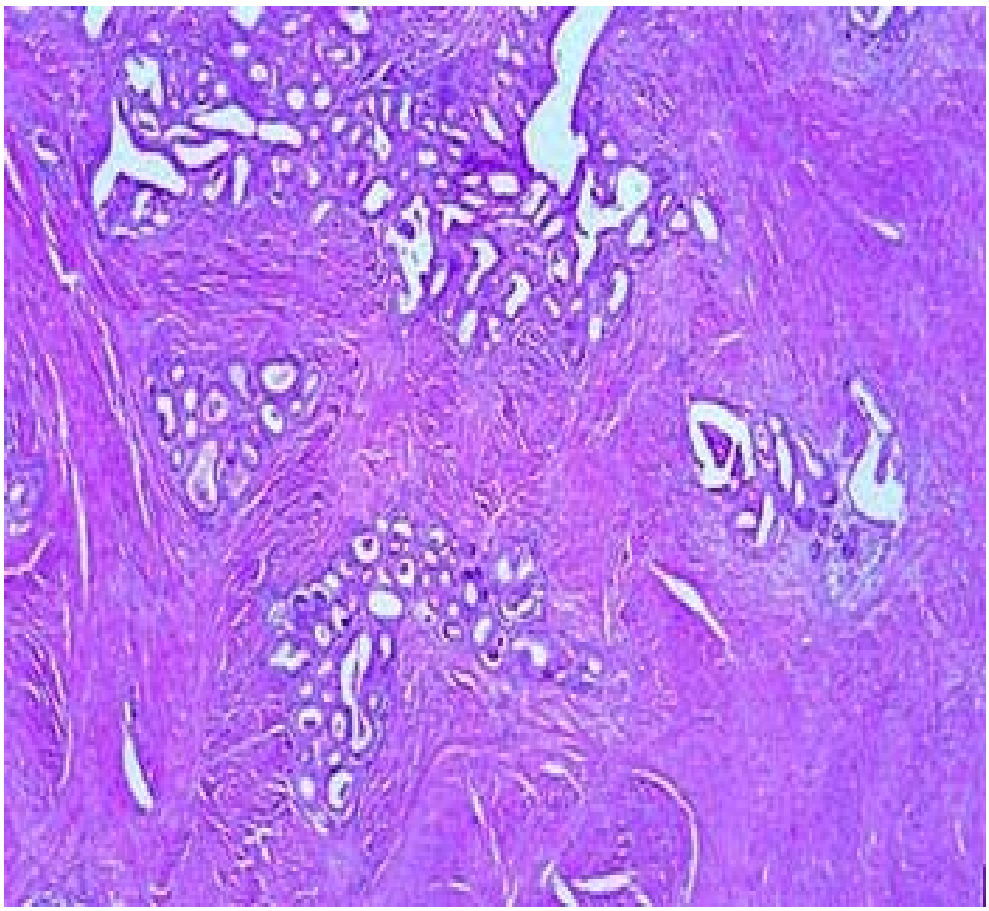
Figure (6) Endometrial adenocarcinoma (endometrioid type)



Endometrial adenocarcinoma (endometrioid type,well differentiated)

(H & E, 40x objective)

Figure (7) Endometrial adenocarcinoma showing myometrial invasion



Endometrial adenocarcinoma showing myometrial invasion (H & E 10x objective).

DISCUSSION

PMB is a common problem in both hospital and general settings. Representing 5 % of all gynaecologic outpatients attendance. Patients with postmenopausal bleeding have 10-15% chance to develop endometrial carcinoma.

This study is a retrospective crossectional study designated to describe histopathological patterns of PMB in endometrial biopsies. It was carried out in the period 2009-june2010 and included 146 endometrial biopsies taken from women presenting with PMB. 12.3% of biopsies were in adequate for interpretation.

The majority of histopathological patterns were benign lesions(84%),much higher than the reported incidence in developed countries where benign pathology was found to be >60 %,and of **Pamela et** al from India with a prevalence of 63.6%.This may be attributed to the contribution of other benign lesions in this study not included in previous studies e.g. chronic endometritis.

In this study endometrial polyps were the predominant histologic finding with a figure of 19.9%. That is higher than that reported by Kauser, Jillani, Razia Bhadour, Kharo et al incidence of 12%(46),with hypperplastic polyps being the most frequent type. The malignancy risk of

endometrial polyps in post menopausal women was correlated to the presence or absence of abnormal uterine bleeding.[47]

Armando et al., concluded that premalignant lesions were associated with age and PMB.[48]Endometrial hyperplasia with or without atypia is considered to be a precursor of endometrial carcinoma, and concurrent carcinoma at rates ranging 17-52%(21). In this study incidence of endometrial hyperplasia was found to be 17.8% that is comparable to reported incidence of 14.3% in a study by Veena, et al that included 108 cases with PMB.[49]

The most recent prevalence of endometrial cancer is quoted to be around9.9-11% .in the present study, endometrial carcinoma accounts for15.8% which is higher than the reported incidence of Youssef et al.,[50] with endometrioid adenocarcinoma being the most frequent type (73.9/%). Papillary serous carcinoma constituted 4.3%of endometrial cancer, which is almost consistent with the incidence written in the literature of 5-10%. The incidence of atrophic endometrium in this study was found to be 7.5%. This can easily be explained on the background of physiological change during menopause.[1]

The exact cause of bleeding from atrophic endometrium isn't known. It is postulated to be due to anatomic vascular variation or local abnormal haemostatic mechanism.[51] In the present study, proliferative endometrium

accounts for 11%, that’s higher as compared to the reported incidence of Veena, et al., was 8.6%.

Proliferative endomtrium may be due to fluctuating levels of progesterone from follicular remnants, the effects persist up to 15years after cessation of menses.[52]

Although chronic endometritis is a disorder of re productive years,it was diagnosed in 4.5% of biopsies.

Chronic endometritis in postmenopausal years maybe attributed to endometrial inflammation following instrumentation such as prior biopsy or organic lesions such as hyperplasia, polyp or carcinoma.[12]

CONCLUSION

- The majority of histopathological findings in PMB were benign lesions (71.9%), among benign lesions; endometrial polyps were the most frequent pattern.
- There was a high incidence of endometrial hyperplasia (17.8%), however, all were non atypical hyperplasia.
- The malignancy risk of endometrial cancer was found to be 15.8%.
- Endometrial adenocarcinoma was the commonest endometrial cancer (73.9%), 41.4% were poorly differentiated adenocarcinoma.
- This study showed a high prevalence of endometrial biopsies inadequate for interpretation (12.3%).

RECOMMENDATIONS

- PMB is a serious problem not to be underestimated.
- More prospective large scale studies are recommended to shed light on histopathological findings in PMB.
- Medical treatment and regular follow up by endometrial sampling is recommended for all cases of endometrial hyperplasia, in order to detect and diagnose endometrial cancer at an early stage.
- Provision of guidelines and protocol for endometrial sampling as the definite diagnosis and staging of endometrial cancer rely on histopathological examination.

REFERENCES

1. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas 1992 Jan; 14(2):103-15
2. Cramer DW, Harlow BL, Xu H, et al. Cross-sectional and case-controlled analyses of the association between smoking and early menopause. Maturitas. 1995 Sep; 22(2):79-87.
3. Santoro N, Brown JR, Adel T, et al. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab 1996 Apr; 81(4): 1495-501.
4. Lenton EA, de Kretser DM, Woodward AJ, et al. Inhibin concentrations throughout the menstrual cycles of normal, infertile, and older women compared with those during spontaneous conception cycles. J Clin Endocrinol Metab 1991 Dec; 73(6):1180-90.
5. Smith KE, Judd HL. Menopause and postmenopause. In: DeCherney AH, Pernoll ML (editors). Current Obstetric and Gynecologic Diagnosis and Treatment. 8th ed. London: Appleton & Lange; 1994. P. 1030-1050.
6. Eastell R. Treatment of postmenopausal osteoporosis. N Engl J Med 1998 Mar 12; 338(11):736-46.

7. Kannel WB, Hjortland MC, McNamara PM, et al. Menopause and risk of cardiovascular disease: the Framingham study. Ann Intern Med 1976 Oct; 85(4): 447-52.
8. Darling GM, Johns JA, McCloud PI, et al. Estrogen and progestin compared with simvastatin for hypercholesterolemia in postmenopausal women. N Engl J Med. Aug 28 1997; 337(9): 595-601.
9. Magnusson C, Holmberg L, Norden T, et al. Prognostic characteristics in breast cancers after hormone replacement therapy. Breast Cancer Res Treat 1996; 38(3): 325-34.
10. Armstrong K, Eisen A, Weber B. Assessing the risk of breast cancer. N Engl J Med 2000 Feb 24; 342(8): 564-71.
11. Tang MX, Jacobs D, Stern Y, et al. Effect of estrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996 Aug 17; 348(9025): 429-32.
12. Micheal T, Mazur R, Kurman J. Diagnosis of endometrial biopsies and Curetting, 4th editin Spriger-Verlage.
13. Fleisher A, Gordon A, Entman S, Kepple D. Transvaginal scanning of the endometrium. J Clin Ultrasound 1990; 18: 337–349.
14. Granberg S, Wikland M, Karlsson B, Norström A, Friberg L-G. Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. Am J Obstet Gynecol 1991; 164: 47–52.

15. Speroffl-Glass RH, Kase NG. Clinical gynaecologic Endocrinology and infertility, 4th edition. Baltimore: Williams and Willikins; 1989.
16. Merril JA. The interpretation of endometrial biopsies. Clinical Obstet Gynecol 1991.
17. Stovall TG, Soloman SK, Ling FW. Endometrial sampling prior to hysterectomy. Obstet Gynecol 1989; 73: 405-406.
18. Kurman RJ, Norris HJ. Endometrial hyperplasia and related cellular change. In: Kurman RJ (editor) Blaustein's pathology of Female Genital Tract, 4th edition. New York: Sringer-Verlag; 1994. P. 411-437.
19. Lee KR, Scully RE. Complex endometrial hyperplasia and carcinoma in adolescents and young women 15-20 years of age. A report of 10 cases. Int Gyneclo Pathol 1989; 8: 201-213.
20. Horn LC, Schnurrbusch U, Bilek K, Hentschel B, Einenkel J. Risk of progression in complex and atypical endometrial hyperplasia: clinicopathologic analysis in cases with and without progesterone treatment. Int J Gynecol Cancer 2004 Mar-Apr; 14(2): 348-53.
21. Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer J 2006 Feb 15; 106(4):812-9.
22. Zaino RJ, Kauderer J, Trimble CL, Silverberg SG, Curtin JP, Lim PC. Reproducibility of the diagnosis of atypical endometrial

hyperplasia: a Gynecologic Oncology Group study. Cancer J 2006 Feb 15; 106(4): 804-11.

23. Kendall BS, Ronnett BM, Isacson C, Cho KR, Hedrick L, Diener-West M. Reproducibility of the diagnosis of endometrial hyperplasia, atypical hyperplasia, and well-differentiated carcinoma. Am J Surg Pathol. 1998 Aug; 22(8): 1012-9.

24. The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. 1996 Feb 7; 275(5): 370-5.

25. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. Mod Pathol. Mar 2000; 13(3): 295-308.

26. Maxwell GL, Risinger JI, Gumbs C, Shaw H, Bentley RC, Barrett JC, et al. Mutation of the PTEN tumor suppressor gene in endometrial hyperplasias. Cancer Res J 1998*;* 58:2500-*3.*

27. Wu HH, Schuetz MJ Cramer H. Significance of benign endometrial cells in Pap smears from postmenopausal women. J Reprod Med 2001 Sep; 46(9): 795-8.

28. Reed S, Voigt L, Newton K, Garcia R, Allison H, Epplein M, et al. Progestin therapy of complex endometrial hyperplasia with and without atypia. Obstet Gynecol 2009 March; 113: 655-662.

29. Gambrell RD Jr. Progestogens in estrogen-replacement therapy. Clin Obstet Gynecol 1995 Dec; 38(4): 890-901.
30. Ellison LH, et al. The female genital tract. In: Kumar V, et al., (editors) rabbin and cotran pathologic basis of disease, 8th edition. Philadelphia: Saunders; Elsevier 2009.
31. Surveillance, Epidemiology, and End Results (SEER) Program. SEER Database: Incidence - SEER 9 Regs Public-Use. National Cancer Institute, DCCPS, Surveillance Research Program.
32. Bernstein L, Deapen D, Cerhan JR, et al. Tamoxifen therapy for breast cancer and endometrial cancer risk. J Natl Cancer Inst. Oct 6 1999; 91 (19): 1654-62.
33. McCLuggage WG. Gynecological specimen In histopathology Specimen: in: Derek C. Allen and R. Lain R (editors) Clinical, Pathological and Laboratory Aspects. Cameron: Springer-Verlag; 2004.
34. Stanley J, Robby RJ, Kurman MJ. The female reproductive system. In: Rubin's Pathology (Clinico pathologic foundation of Medicine.), 4th ed Lippincott: Williams and Wilikins; 2005.
35. Diasia PJ, Creasman WT. Clinical Gnecologiconcology, 4th edition Stlouis: Mosby-year book; 1993.
36. Smith M, McCarteny AJ. Occult: high risk endometrial cancer. Gynecol Oncol 1985; 22: 154-161.

37. Kurman RJ, Mazur MT. Benign diseases of the endometrium E. In: Kurman RJ (editor). Blaustein's pathology of Female Genital Tract, 4th edition. New York: Sringer-Verlag; 1994. P. 411-437.

38. Vanbogaert LJ. Clinicopathological findings in endometrial polyps. Obstet Gynecol 1988; 71: 771-773.

39. Schlaen I, Bergeron C, Ferenczy A, Wong P, Naves A, et al. Endometrial polyps: a study of 204 cases. Sur Path1 988; 1: 375-382.

40. Young RH, Treger T, Scully RE. A typical polypoid adenomyoma of the uterous. a report of 27 cases. Am J Clin Pathol 1986; 86: 139-145.

41. Clement PB, Young RH. A typical polypoid adenomyoma of the uterous associated with turner syndrome. Int J Gynecol Pathol 1987; 6: 104-113.

42. Green-wood SM, Moran JJ. Chronic endometritis: morphologic and clinical observations. Obstet Gynecol 1981; 58: 176-184.

43. Schaefer G, Marcus RS, Kramer EE. Postmenopausal endometrial tuberculosis. Am J Obstet Gynecol 1972; 112: 681-687.

44. Kurman RJ, Mazur MT. Benign diseases of the endometrium. In: Kurman RJ (editor) Blaustein's pathology of Female Genital Tract, 4th edition. New York: Sringer-Verlag; 1994. P.367-409.

45. Winkler B, Reumann W, Miato M, Gallo L, Richart RM, et al. Chlamydial endometritis a histological and immunohistochemical analysis. Am J Surg Pathol 1984; 8:771-778.

46. Kauser J, Razia Bahadur K, Safia M, Maqsood AS. Acta Obste Gynecol Scandinavia 2009; 88 (5): P. 618-620.
47. Armando Antunes-Junior, Physician, Universidade Estadual de Campinas, Campinas, Sao Paulo, Brazil, on October 4/2007
48. Veena SN, Jyoti DR, Kusum DJ. Histopathological findings in women with postmenopausal bleeding.
49. Youssef A, Ben AN, Gara MF. Postmenopausal uterine bleeding: Analatyical study of about 65cases.Tunis Med 2005; 83: 453-65.
50. Thomas G, Sonja K, Guillaume H, Lars-ake M. Histopathological findings in women with postmenopausal bleeding. Br J of Obstet and Gynec 1995; 102: 133-36.

University of Khartoum

Faculty of Medicine

Postgraduate Medical Studies Board

Questionnaire

Histopathological patterns of endometrial biopsies in patients with postmenopausal bleeding (histopathological study)

Date: ..... **lab number:** .....

Clinical data:

Age: .....

Clinical presentation: .....

Procedure of endometrial sampling: .....

Dilatation and curettage (D&C)

Hysterectomy .....

Polypectomy .....

Histological findings:

Microscopy: .....

Histological type .....

Grading of endometrial adenocarcinoma:

Well .....

Moderate .....

Poor differentiated: .....

WHO histological classification of tumours of the uterine corpus

Epithelial tumours and related lesions

- Endometrial carcinoma
  - Endometrioid adenocarcinoma 8380/3
    - Variant with squamous differentiation 8570/3
    - Villoglandular variant 8262/3
    - Secretory variant 8382/3
    - Ciliated cell variant 8383/3
  - Mucinous adenocarcinoma 8480/3
  - Serous adenocarcinoma 8441/3
  - Clear cell adenocarcinoma 8310/3
  - Mixed cell adenocarcinoma 8323/3
  - Squamous cell carcinoma 8070/3
  - Transitional cell carcinoma 8120/3
  - Small cell carcinoma 8041/3
  - Undifferentiated carcinoma 8020/3
  - Others
- Endometrial hyperplasia
  - Nonatypical hyperplasia
    - Simple
    - Complex (adenomatous)
  - Atypical hyperplasia
    - Simple
    - Complex
- Endometrial polyp
- Tamoxifen-related lesions

Mesenchymal tumours

- Endometrial stromal and related tumours
  - Endometrial stromal sarcoma, low grade 8931/3
  - Endometrial stromal nodule 8930/0
  - Undifferentiated endometrial sarcoma 8930/3
- Smooth muscle tumours
  - Leiomyosarcoma 8890/3
    - Epithelioid variant 8891/3
    - Myxoid variant 8896/3
  - Smooth muscle tumour of uncertain malignant potential 8897/1
  - Leiomyoma, not otherwise specified 8890/0
    - Histological variants
      - Mitotically active variant
      - Cellular variant 8892/0
      - Haemorrhagic cellular variant
      - Epithelioid variant 8891/0
      - Myxoid 8896/0
      - Atypical variant 8893/0
      - Lipoleiomyoma variant 8890/0
    - Growth pattern variants
      - Diffuse leiomyomatosis 8890/1
      - Dissectiing leiomyoma
      - Intravenous leiomyomatosis 8890/1
      - Metastasizing leiomyoma 8898/1
- Miscellaneous mesenchymal tumours
  - Mixed endometrial stromal and smooth muscle tumour
  - Perivascular epithelioid cell tumour
  - Adenomatoid tumour 9054/0
  - Other malignant mesenchymal tumours
  - Other benign mesenchymal tumours

Mixed epithelial and mesenchymal tumours

- Carcinosarcoma (malignant müllerian mixed tumour; metaplastic carcinoma) 8980/3
- Adenosarcoma 8933/3
- Carcinofibroma 8934/3
- Adenofibroma 9013/0
- Adenomyoma 8932/0
  - Atypical polypoid variant 8932/0

Gestational trophoblastic disease

- Trophoblastic neoplasms
  - Choriocarcinoma 9100/3
  - Placental site trophoblastic tumour 9104/1
  - Epithelioid trophoblastic tumour 9105/3
- Molar pregnancies
  - Hydatidiform mole 9100/0
    - Complete 9100/0
    - Partial 9103/0
    - Invasive 9100/1
    - Metastatic 9100/1
- Non-neoplastic, non-molar trophoblastic lesions
  - Placental site nodule and plaque
  - Exaggerated placental site

Miscellaneous tumours

- Sex cord-like tumours
- Neuroectodermal tumours
- Melanotic paraganglioma
- Tumours of germ cell type
- Others

Lymphoid and haematopoetic tumours

- Malignant lymphoma (specify type)
- Leukaemia (specify type)

Secondary tumours

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {921} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.